IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Jeffrey Hubbell, Jason Schense, Andreas Zisch, and Heike Hall

Serial No.: 10/650,509 Art Unit: 1651

Filed: August 27, 2003 Examiner: Leon B. Lankford, Jr.

For: *ENZYME-MEDIATED MODIFICATION OF FIBRIN FOR TISSUE ENGINEERING*

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35 in the Office Action mailed on October 5, 2007, in the above-identified patent application. A Notice of Appeal was filed on February 5, 2008, with a Petition for Extension of Time for one month. Submitted with this Appeal Brief is a Petition for Extension of Time to extend period for filing a response two months, up to and including June 5, 2008. The Commissioner is hereby authorized to charge $970.00, the sum of the fee for filing an Appeal Brief ($510) and a Petition for a Two Month Extension of Time ($460) for a large entity, to Deposit Account No. 50-3129.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTIES IN INTEREST

The real parties in interest of this application are the assignee, California Institute of Technology, and the licensees, Kuros Biosurgery AG, Straumann Holding AG and Baxter Healthcare.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

Claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35 are pending, rejected, and on appeal. Claims 6, 8, 15, 23-25, and 31-33 have been cancelled. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

An amendment after the final office action was filed on March 28, 2008. In the Advisory Action mailed May 13, 2008, the Examiner indicated that this amendment will be entered (*see* Advisory Action continuation sheet). The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 defines a composition comprising a matrix and a bidomain protein or peptide having an amino acid sequence that comprises a transglutaminase substrate domain and a polypeptide growth factor, wherein the protein or peptide is covalently bound to the matrix by the transglutaminase substrate domain (page 5, lines 22-26). Claim 2 depends on claim 1 and specifies that the matrix comprises fibrin (page 5, lines 22-26). . Claim 3 depends on claim 2 and specifies that the transglutaminase substrate domain is a Factor XIIIa substrate domain (page 5, lines 22-26). Claim 4 depends on claim 3 and specifies that the Factor XIIIa substrate domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15, and combinations and bioactive fragments thereof (page 13, lines 7-9). Claim 5 depends on claim 3 and specifies that the Factor XIIIa comprises SEQ ID NO: 15 (page 13, lines 7-9). Claim 7 depends on claim 1 and specifies that the growth factor comprises an amino acid sequence selected from the group consisting of TGF-β1, BMP 2, $VEGF_{121}$, PDGF AB, L1Ig6, and combinations and bioactive fragments thereof (page 5, line 29 to page 6, line 1, and page 10, lines 6-8). Claim 9 depends on claim 1 and specifies that the growth factor is selected from the group consisting of VEGF, a growth factor from the TGF-β superfamily, PDGF, IGF, and ephrin (page 5, lines 26-28).

Independent claim 10 defines a method of attaching a polypeptide growth factor to a matrix, comprising producing a bidomain peptide or protein comprising a growth factor and a transglutaminase substrate domain; and exposing the matrix to a transglutaminase to covalently

couple the bidomain peptide or protein to the matrix and crosslink the matrix (page 13, lines 25-28). Claim 11 depends on claim 10 and specifies that the matrix comprises fibrin (*see* page 5, lines 22-26). Claim 12 depends on claim 10 and specifies that the transglutaminase substrate domain is a Factor XIIIa substrate domain and the transglutaminase is Factor XIIIa (*see* page 13, line 28 to page 14, line 2). Claim 13 depends on claim 12 and specifies that the Factor XIIIa substrate comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15, and a combination or bioactive peptide fragment thereof. Claim 14 depends on claim 13 and specifies that Factor XIIIa substrate comprises SEQ ID NO: 15 (*see* page 13, lines 7-9). Claim 15 depends on claim 10 and specifies that the growth factor is selected from the group consisting of VEGF, growth factors from the TGF-β superfamily, PDGF, IGF, and ephrin; claim 17 depends on claim 10 and specifies that the growth factor contains an amino acid sequence selected from the group consisting of TGF-β1, BMP 2; $VEGF_{121}$, PDGF AB, L1Ig6, and a combination or bioactive peptide fragment thereof (*see* page 5, line 29 to page 6, line 1, and page 10, lines 6-8).

Independent claim 18 defines a bidomain protein or peptide comprising a transglutaminase substrate domain and a polypeptide growth factor (*see* page 5, lines 22-24). Claim 19 depends on claim 18 and specifies that the protein or peptide is a recombinant or synthetic protein or peptide (*see* page 5, lines 22-23). Claim 20 depends on claim 18 and specifies that the transglutaminase substrate domain is a Factor XIIIa substrate domain (page 5, lines 22-26 and page 13, lines 4-6). Claim 21 depends on claim 20 and specifies that the Factor

XIIIa substrate domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO: 15, and combinations and bioactive fragments thereof (*see* page 13, lines 7-9). Claim 22 depends on claim 21 and specifies that Factor XIIIa substrate comprises SEQ ID NO: 15 (*see* page 13, lines 7-9). Claim 26 depends on claim 18 and specifies that the growth factor is selected from the group consisting of VEGF, a growth factor from the TGF-β superfamily, PDGF, IGF, and ephrin. Claim 27 depends on claim 26 and specifies that the growth factor is selected from the group consisting of TGF-β1, $VEGF_{121}$, PDGF AB, BMP 2, and L1Ig6 (claim 27) (*see* page 5, line 29 to page 6, line 1, and page 10, lines 6-8).

Independent claim 28 defines a matrix material for forming a gel comprising (i) a bidomain protein or peptide comprising a transglutaminase domain and a polypeptide growth factor, (ii) fibrinogen, (iii) factor XIIIa, and (iv) thrombin (*see* page 5, lines 22-26 and page 14, lines 9-21). Claim 29 depends on claim 28 and specifies that the transglutaminase substrate domain is a Factor XIIIa substrate domain (*see* page 13, lines 4-6). Claim 30 depends on claim 29 and specifies that that the Factor XIIIa substrate domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15, and combinations and bioactive fragments thereof (*see* page 13, lines 7-9). Claim 34 depends on claim 28 and specifies that that the growth factor is selected from the group consisting of VEGF, a growth factor from the TGF-β superfamily, PDGF, IGF, and ephrin. Claim 35 depends on claim 34 and specifies that the growth factor is selected from the group

consisting of TGF-β1, $VEGF_{121}$, PDGF AB, BMP 2, and L1Ig6 (claim 35) (*see* page 5, line 29 to page 6, line 1, and page 10, lines 6-8).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are whether claims 1-35 (now claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35) are patentable under the judicially created doctrine of nonstatutory double patenting in view claims 1-39 of U.S. Patent No. 6,331,422 to Hubbell, *et al.* ("the '422 patent"), claims 1-18 of U.S. Patent No. 6,607,740 to Hubbell, *et al.* ("the '740 patent"), 1-20 of U.S. Patent No. 7,247,609 to Lutolf, *et al.* ("the '609 patent"), and/or claims 1-25 of U.S. Serial No. 10/323,046 by Hubbell, *et al.* ("the '046 application").

(7) ARGUMENTS

(a) Rejection of claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35 under the judicially created doctrine of obviousness type double patenting.

Legal Standard

Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent. *In re Van Ornum*, 214 U.S.P.Q. 761 (C.C.P.A.1982); *In re Zickendraht*, 138 U.S.P.Q. 22 (C.C.P.A. 1963). As discussed below, this situation can only arise if there is common ownership.

The patent rules make clear the necessity for common ownership; and the MPEP affirms this requirement.

37 C.F.R. § 1.321(c)(3) requires that "a terminal disclaimer filed to obviate a judicially created double patenting rejection in a patent application... must...include a provision that any patent granted on that application...shall be enforceable only for and during such period that said patent is **commonly owned** with the application or patent which formed the basis for the rejection." (emphasis added).

37 C.F.R. 1.78(c) provides "If an application or a patent under reexamination and at least one other application naming different inventors are owned by the same person and contain conflicting claims, and [...] if the claimed inventions were **commonly owned**, or subject to an obligation of assignment to the same person, at the time the later invention was made, the conflicting claims may be rejected under the doctrine of double patenting in view of such commonly owned or assigned applications or patents under reexamination." (emphasis added).

There is only one exception to the requirement for common ownership, **where there is a joint research agreement, which is not applicable here**. In describing the analysis that an Examiner must conduct to determine if an obviousness-type double patenting rejection is proper, the MPEP explains:

> Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in **a commonly owned patent, or a non-commonly owned patent but subject to a joint research agreement as set forth in 35 U.S.C.**

103(c)(2) and (3), when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent.

M.P.E.P 804 (II)(B)(1) (emphasis added).

The M.P.E.P elaborates on the common ownership requirement in section 804.03. In this section, the M.P.E.P notes that "[c]laims in commonly owned applications of different inventive entities may be rejected on the ground of double patenting." The M.P.E.P. continues by referring to only one situation in which non-commonly owned applications or an application and a granted patent may be rejected under obviousness-type double patenting. This situation is when the claims define inventions resulting from activities undertaken within the scope of a joint research agreement. The M.P.E.P. states "Claims may also be rejected on the grounds of nonstatutory double patenting in certain **non-commonly owned applications that claim inventions resulting from activities undertaken with the scope of a joint research agreement as defined in 35 U.S.C. 103(c)(3).**" (emphasis added).

The M.P.E.P. provides further guidance to Examiners regarding when to make a double patenting rejection. The M.P.E.P. explains that when the facts support both rejections, "both a double patenting rejection **based on common ownership** and a rejection based on 35 U.S.C. 102(e)/ 103 prior art" should be made by the Examiner. M.P.E.P §804.03(II)(C) (emphasis added) However, if there is no common ownership, the M.P.E.P. does not instruct the Examiner to make a double patenting rejection. Rather, the M.P.E.P. notes that only a rejection under 35 U.S.C. 102(e)/ 103 prior art should be made first. "Until applicant has established that a

reference is disqualified as prior art under the joint research agreement exclusion of 35 U.S.C. 103(c), the examiner should NOT apply a double patenting rejection based on a joint research agreement." M.P.E.P §804.03(II)(C) (emphasis in original).

Accordingly, it is clear that this rejection is legally improper with respect to U.S. Patent No. 7,247,609 to Lutolf, *et al.*, and pending application No. 10/323,046 to Hubbell, *et al.*, which do not share common ownership with the present application. Thus, the only possible rejection in view of U.S. Patent No. 7,247,609 to Lutolf, *et al.* and/or pending application No. 10/323,046 to Hubbell, *et al.*, could have been made under 35 U.S.C. §102 and/or §103. However, as discussed below, the claims are novel and inventive in view of U.S. Patent No. 7,247,609 to Lutolf, *et al.*, and/or pending application No. 10/323,046 to Hubbell, *et al.*

(a) Claims 1-39 of U.S. Patent No. 6,331,422 to Hubbell, et al. ("the '422 patent")

Appellants will submit a terminal disclaimer, without prejudice, to overcome the double patenting rejection with respect to claims 1-39 of the '422 patent when the claims are determined to be otherwise patentable.

(b) Claims 1-35 of U.S. Patent No. 6,607,740 to Hubbell, et al. ("the '740 patent")

Appellants will submit a terminal disclaimer, without prejudice, to overcome the double patenting rejection with respect to claims 1-35 of the '740 patent when the claims are determined to be otherwise patentable.

(c) U.S. Patent No. 7,247,609 to Lutolf, et al. ("the '609 patent")

Claims 1-35 were rejected under the judicially created doctrine of nonstatutory double patenting as obvious in view claims 1-20 of U.S. Patent No. 7,247,609 ("the '609 patent"). Appellants respectfully traverse this rejection for at least the reasons set forth below.

(i) The Rejection is legally improper

There is no common ownership

The '609 patent is jointly owned by Eidgenössische Technische Hochschule Zürich and Universität Zürich. The pending application is owned by California Institute of Technology. Thus the '609 patent and the pending application are not commonly owned. Additionally, the claims in the '609 patent and the claims in the pending application are not the result of research that was the subject to a joint research agreement. Therefore the rejection for obviousness-type double patenting over claims 1-20 of the '609 patent is a legally improper rejection.

Even if the rejection was a proper rejection, the present claims are patentably distinct from claims 1-20 of the '609 patent as shown by the claim-by-claim analysis below.

(ii) Claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35 are not obvious in view of claims 1-20 of the '609 patent

(a) The scope of claims 1-20 of the '609 patent

Independent claim 1 defines a fusion peptide, comprising a first domain comprising a PTH, a second domain comprising a covalently crosslinkable substrate domain, wherein the covalently crosslinkable substrate domain is transglutaminase substrate domain, and an

enzymatic degradation site between the first and the second domain. Claims 2-6 depend directly or indirectly from claim 1. Dependent claims 2 and 3 further define the PTH. Dependent claims 4 and 5 further define the transglutaminase substrate domain. Dependent claim 6 further defines the enzymatic degradation site.

Independent claim 7 defines a kit comprising a fusion peptide, comprising a first domain comprising a PTH, a second domain comprising a covalently crosslinkable substrate domain, wherein the covalently crosslinkable substrate domain is transglutaminase substrate domain, and an enzymatic degradation site between the first and the second domain. Dependent claims 8-13 depend directly and indirectly from claim 7. Dependent claim 8 specifies that the kit further comprises fibrinogen, thrombin and a calcium source. Dependent claim 9 specifies that the kit further comprises a crosslinking enzyme. Dependent claim 10 further defines the PTH. Dependent claims 11 and 12 further define the transglutaminase substrate domain. Dependent claim 13 further defines the enzymatic degradation site.

Independent claim 14 defines a matrix suitable for cellular growth or in-growth, wherein at least one fusion peptide is covalently linked to the matrix, wherein the fusion peptide comprises a first domain comprising a PTH, a second domain comprising a covalently crosslinkable substrate domain, wherein the covalently crosslinkable substrate domain is transglutaminase substrate domain, and an enzymatic degradation site between the first and the second domain, wherein the fusion peptide is linked to the matrix by the second domain. Dependent claims 15-19 depend directly and indirectly from claim 14. Dependent claim 15

further defines the PTH. Dependent claims 16 and 17 further define the transglutaminase substrate domain. Dependent claim 18 specifies that the matrix comprises fibrin. Dependent claim 19 specifies that the matrix comprises polyethylene glycol.

Independent claim 20 defines a method for making a matrix comprising providing at least one matrix material capable of forming a crosslinked matrix, wherein the matrix material is selected from the group consisting of proteins and synthetic materials, adding a fusion peptide to the matrix material wherein the fusion peptide comprises a first domain comprising a PTH, a second domain comprising a substrate domain capable of being covalently crosslinked to a matrix, wherein the covalently crosslinkable substrate domain is transglutaminase substrate domain, and an enzymatic degradation site between the first and the second domain, and crosslinking the matrix material, such that the fusion peptide is linked to the matrix through the second domain.

(b) Differences between claims 1-20 of the '609 patent and claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35 of the present application.

Claims 1-5 of the present application

Claims 1-20 of the '609 patent do not define the claimed composition comprising a matrix and a bidomain protein that comprises a polypeptide growth factor. Furthermore, claims 1-5 of the present application do not require an enzymatic degradation site between the two domains of the bidomain peptide. Thus, the bidomain peptide recited in claims 1-5 of the present application and the bidomain peptide recited in claims 1-20 of the '609 patent are structurally

different. The Examiner has provided no reason why one of ordinary skill in the art would modify the bidomain peptide recited in claims 1-20 of the '609 patent to replace the PTH recited in the claims with a growth factor, and to remove the enzyme degradation site. However, if such a modification were made, it would change the mode of operation of the bidomain peptide recited in claims 1-20 of the '609 patent. For example, the degradation site required by all of the claims in the '609 patent allows for a more controlled release of PTH from the matrix compared to release in the absence of the degradation site. The degradation site allows for the PTH to be released via cellular processes, such as via enzymes released from cells that invade the matrix, instead of solely via diffusion out of the matrix (*see e.g.* the'609 patent, col. 14, lines 26-29). Such a modification is not permissible since removal of the degradation site would materially change the mode of operation of the fusion peptides, kits, matrices and methods defined by claims 1-20 of the '609 patent (*see* MPEP §2143.01(V) and (VI)).

Claims 7 and 9 of the present application

For at least set forth above with respect to claims 1-5, claims 1-20 of the '609 patent do not make obvious claims 7 and 9 of the presente application. Additionally, claims 1-20 of the '609 patent do not recite any of the growth factors listed in claims 7 and 9. One of ordinary skill in the art would not modify fusion peptides, kits, matrices and methods defined by claims 1-20 of the '609 patent to replace the PTH in the first domain with the growth factors recited in claims 7 and 9.

Claims 10-14 and 16-17 of the present application

Independent claim 10 and dependent claims 11-14, 16 and 17 define a method of attaching a polypeptide growth factor to a matrix, comprising producing a bidomain peptide or protein comprising a growth factor and a transglutaminase substrate domain; and exposing the matrix to a transglutaminase to covalently couple the bidomain peptide or protein to the matrix and crosslink the matrix. As stated above with respect to claims 1-5 of the present application, the claimed method does note require a growth factor with an enzymatic degradation site. A modification to remove the degradation site required by claims 1-20 of the '609 patent would change the mode of operation of the fusion peptide required by claims 1-20 of the '609 patent.

Claims 18-22 of the present application

Independent claim 18 and dependent claims 19-22 define a bidomain protein or peptide comprising a transglutaminase substrate domain and a polypeptide growth factor. Claims 18-22 do not require an enzymatic cleavage site. The Examiner has provided no reason why one of ordinary skill in the art would modify the fusion protein required by claims 1-20 of the '609 patent ,which requires PTH and an enzymatic cleavage site, to arrive at the claimed bidomain peptide which does not require an enzymatic cleavage site and comprises a growth factor. Furthermore, as discussed above with respect to claims 1-5 of the present application, such a modification is not permissible since removal of the degradation site would materially change the mode of operation of the fusion peptides, kits, matrices and methods defined by claims 1-20 of the '609 patent (*see* MPEP § 2143.01 (V) and (VI)).

Claims 26 and 27 of the present application

Claims 26 and 27 depend from claim 18 directly and indirectly, respectively, and further define the growth factor. For at least the reasons set forth above with respect to claims 18-22, claims 1-20 of the '609 patent do not make do not make obvious claims 26 and 27. Additionally, claims 1-20 of the '609 patent do not recite the specific growth factors listed in claims 26 and 27. One of ordinary skill in the art would not modify fusion peptides, kits, matrices and methods defined by claims 1-20 of the '609 patent to replace the PTH in the first domain with the growth factors recited in claims 26 and 27.

Claims 28-30 of the present application

Claims 1-20 of the '609 patent do not recite all of the limitations recited in claims 28-30. Independent claim 28 and dependent claims 29, and 30 define a matrix material that requires a peptide which is structurally different from the fusion peptide required by claims 1-20 of the '609 patent. The Examiner has provided no reason why one of ordinary skill in the art would extrapolate from the fusion protein required by claims 1-20 of the '609 patent, which requires PTH and an enzymatic cleavage site, to arrive at the claimed matrix material which does not require an enzymatic cleavage site and comprises a growth factor. Furthermore, as discussed above with respect to claims 1-5 of the present application, such a modification is not permissible since removal of the degradation site would materially change the mode of operation of the fusion peptides, kits, matrices and methods defined by claims 1-20 of the '609 patent (*see* MPEP § 2143.01 (V) and (VI)).

Claims 34 and 35 of the present application

Claims 34 and 35 depend from claim 28 directly and indirectly, respectively, and further define the growth factor. For at least the reasons set forth above with respect to claims 28-30, claims 1-20 of the '609 patent do not make do not make obvious claims 34 and 35. Additionally, claims 1-20 of the '609 patent do not recite the specific growth factors listed in claims 34 and 35. One of ordinary skill in the art would not modify fusion peptides, kits, matrices and methods defined by claims 1-20 of the '609 patent to replace the PTH in the first domain with the growth factors recited in claims 34 and 35.

For at least the reasons discussed in the claim-by-claim analysis above, claims 1-5, 7, 9-14, 16-22, 26-30, 34, and 35 of the present application are non-obvious in view of claims 1-20 of the '609 patent.

As explained above, the claims in the present application could only be rejected under 35 U.S.C. §102 and/or §103. However, the '609 patent does not anticipate or make obvious the claims of the present application for at least the reasons set forth below.

(iii) Even if a rejection under 35 U.S.C. §102 and/or §103 had been made, the claims are not anticipated or made obvious by the '609 Patent

35 U.S.C. §102 and/or §103 Analysis

The '609 patent is not prior art to the present application

The '609 patent is a continuation-in-part of application No. 10/323,046 filed on December 17, 2002, and a continuation-in-part of application No. 10/024,918, filed on December 18, 2001, now abandoned.

Support for claims 1-5, 10-14, 18-22, and 28-30 of the present application can be found in its priority application, U.S.S.N. 09/057,052, filed April 8, 1998. For example, support for claims 1 and 18 can be found at least at page 6, line 9, page 8, line 8 and page 9, lines 15-17; support for claims 2 and 11 can be found at least at page 2, line 22; support for claims 3, 12, 20, and 29 can be found at least at page 5, lines 20-21; support for claims 4, 5, 13, 14, 21, 22, and 30 can be found at least at page 9, lines 24-26; support for claim 10 can be found at least at page 5, lines 19-25 and page 6, lines 1-2 and 4-6; support for claim 19 can be found at least at page 5, line 20; and support for claim 28 can be found at least at page 6, line 9, page 8, line 8, page 9, lines 15-17 and page 11, lines 27-29 of U.S.S.N. 09/057,052. Thus claims 1-5, 10-14, 18-22 and 28-20 are entitled to a priority date of at least April 8, 1998.

The present application is a continuation of U.S. Serial No. 10/024,918 filed on December 18, 2001. Thus, claims 7, 9, 16, 17, 26, 27, 34 and 35, are entitled to a priority date of at least December 18, 2001.

The earliest priority date that the '609 patent claims is December 18, 2001. Therefore, the '609 patent is not available as prior art in under 35 U.S.C. §102 and/or §103 against claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35 of the present application.

(d) Pending application No. 10/323,046 to Hubbell, et al. (the '046 application)

Claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of claims 1-25 of the '046 application. Appellants respectfully point out that an amendment was filed on April 30, 2008 in the '046 application. Claims 1, 3-6, 9-14, 16-19, and 22-25 are currently pending in the '046 application. Appellants respectfully traverse this rejection for at least the reasons set fort below.

(i) The Rejection is legally improper

There is no common ownership

The '046 application is jointly owned by Eidgenössische Technische Hochschule Zürich and Universität Zürich. The pending application is owned by California Institute of Technology. Thus the '046 application and the pending application are not commonly owned. Additionally, the claims in the '046 application and the claims in the pending application are not the result of research that was the subject to a joint research agreement. Therefore the rejection for obviousness-type double patenting over claims 1, 3-6, 9-14, 16-19, and 22-25 of the '046 application is a legally improper rejection.

Even if the rejection was a proper rejection, the present claims are patentably distinct from claims 1, 3-6, 9-14, 16-19, and 22-25 of the '046 application as shown by the claim-by-claim analysis below.

(ii) Claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35 are not obvious in view of claims 1, 3-6, 9-14, 16-19, and 22-25 of the '046 application

(a) Claims 1, 3-6, 9-14, 16-19, and 22-25 of the '046 application

Independent claim 1 defines a fusion protein comprising a first domain comprising a bioactive peptide, growth factor or hormone, a protein domain comprising a domain which is a substrate for transglutaminase and an enzymatic or hydrolytic cleavage site between the first and the second domain. Dependent claims 3-6 and 9-12 dependent directly or indirectly from claim 1. Claims 3-6 further define the first domain. Claims 9 and 10 further define the second domain. Claims 11 and 12 further define the cleavage site.

Independent claim 13 defines a kit comprising (i) a fusion protein comprising a first domain comprising a bioactive peptide, growth factor or hormone and a second protein domain comprising a substrate for a transglutaminase, and an enzymatic or hydrolytic cleavage site between the first and the second proteins, (ii) fibrinogen, (iii) thrombin, and (iv) a calcium source. Dependent claims 14, 16-19, and 22-25 depend directly or indirectly from claims 13. Claim 14 specifies that the kit further comprises a crosslinking enzyme. Claims 16-19 further define the first domain. Claims 22 and 23 further define the second domain. Claims 24 and 25 further define the cleavage site.

(b) Differences between claims 1, 3-6, 9, 13, 14, 16-19, and 22-25 of the '046 application and claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35 of the present application.

The claims in the '046 application do not define the claimed composition, fusion peptide, method or matrix. All of the claims in the present application require a bidomain peptide which does not require an enzymatic or hydrolytic cleavage site between the first and second domains of the bidomain peptide. Thus, the bidomain peptide recited in the present claims and the fusion peptide required by the claims in the '046 application are structurally different. The Examiner has provided no reason why one of ordinary skill in the art would modify the fusion protein recited in claims 1, 3-6, 9, 13, 14, 16-19, and 22-25 of the '046 application to remove the enzymatic or hydrolytic cleavage site. However, if such a modification were made, it would change the mode of operation of the fusion protein recited in claims 1, 3-6, 9, 13, 14, 16-19, and 22-25 of the '046 application. For example, the enzymatic or hydrolytic cleavage site required by all of the currently pending claims in the '046 application allows for a more controlled release of bioactive peptide, growth factor or hormone from a matrix compared to release in the absence of the enzymatic or hydrolytic cleavage site. The enzymatic or hydrolytic cleavage site allows for the bioactive peptide, growth factor or hormone to be released via cellular processes, such as via enzymes released from cells that invade the matrix, instead of solely via diffusion out of the matrix (*see e.g.* '046 application published as US 2003/0187232 at para. 0027). The inclusion of enzymatic or hydrolytic cleavage site also reduces the amount of total growth factor required to achieve a desired result since its release can be controlled by cellular processes (*see id.*). Such a

modification is not permissible since removal of the enzymatic or hydrolytic cleavage site would materially change the mode of operation of the fusion proteins and kits defined by claims 1, 3-6, 9, 13, 14, 16-19, and 22-25 of the '046 application (*see* MPEP §2143.01(V) and (VI)). Therefore, claims 1, 3-6, 9, 13, 14, 16-19, and 22-25 of the '046 application do not make claims 1-5, 7, 9-14, 16-22, 26-30, 34 and 35 of the present application obvious.

Appellants further note that this is a provisional rejection since the claims in the '046 application are still undergoing prosecution.

(ii) Even if a rejection under 35 U.S.C. § 102 and/or §103 had been made, the claims are not anticipated or made obvious by the '046 application

Analysis under35 U.S.C. § 102 and/or §103

Priority of the '046 application

The '046 application was filed on December 17, 2002 and is a continuation-in-part of U.S.S.N. 09/563,760, filed May 1, 2000 (now U.S. Patent No. 6,894,022), which is a continuation-in-part of U.S.S.N. 09/141,153, filed August 27, 1998 (now abandoned). ' Thus, the earliest priority date that any of the disclosures in the '046 application may be entitled to is August 27, 1998.

The '046 application is not prior art to the present application

As discussed above with respect to the '609 patent, support for claims 1-5, 10-14, 18-22, and 28-30 of the present application can be found in priority application, U.S.S.N. 09/057,052, filed April 8, 1998. Thus claims 1-5, 10-14, 18-22 and 28-20 are entitled to a priority date of at

least April 8, 1998. The earliest priority date that the'046 application is entitled to is August 27, 1998. Therefore, the '046 application is not available as prior art under 35 U.S.C. § 102(a)/103(a) against claims 1-5, 10-14, 18-22, and 28-30 and cannot anticipate or make the claims obvious.

The present application is a continuation of U.S. Serial No. 10/024,918 filed on December 18, 2001. Thus, claims 7, 9, 16, 17, 26, 27, 34 and 35 are entitled to a priority date of at least December 18, 2001.

Although the '046 application discloses specific growth factors, the earliest priority date that this disclosure would be entitled to is the filing date of the '046 application, i.e. December 17, 2002. Thus the '046 application is not available as prior art to claims 7, 9, 16, 17, 26, 27, 34 and 35 of the present application.

Therefore, the '046 application is not available as prior art under 35 U.S.C. § 102(a)/103(a) against claims 1-5, 10-14, 18-22, and 28-30 and cannot anticipate or make the claims obvious.

For the foregoing reasons, Appellants submit that claims 1-5, 7, 9-14, 16-22, 26-30, 34, and 35 are patentable.

Respectfully submitted,

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Claims Appendix: Claims On Appeal

1. (previously presented) A composition comprising a matrix and a bidomain protein or peptide having an amino acid sequence that comprises a transglutaminase substrate domain and a polypeptide growth factor, wherein the protein or peptide is covalently bound to the matrix by the transglutaminase substrate domain.

2. (original) The composition of claim 1 wherein the matrix comprises fibrin.

3. (original) The composition of claim 2 wherein the transglutaminase substrate domain is a Factor XIIIa substrate domain.

4. (original) The composition of claim 3 wherein the Factor XIIIa substrate domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15, and combinations and bioactive fragments thereof.

5. (original) The composition of claim 3 wherein the Factor XIIIa substrate domain comprises an amino acid sequence of SEQ ID NO: 15.

7. (previously presented) The composition of claim 1 wherein the growth factor is selected from the group consisting of TGF-β1, BMP 2, $VEGF_{121}$, PDGF AB, L1Ig6, and combinations and bioactive fragments thereof.

9. (previously presented) The composition of claim 1 wherein the growth factor is selected from the group consisting of VEGF, a growth factor from the TGF-β superfamily, PDGF, IGF, and ephrin.

10. (previously presented) A method of attaching a polypeptide growth factor to a matrix, comprising

producing a bidomain peptide or protein comprising a growth factor and a transglutaminase substrate domain; and

exposing the matrix to a transglutaminase to covalently couple the bidomain peptide or protein to the matrix and crosslink the matrix.

11. (original) The method of claim 10 wherein the matrix comprises fibrin.

12. (previously presented) The method of claim 10 wherein the transglutaminase substrate domain is a Factor XIIIa substrate domain and the transglutaminase is Factor XIIIa.

13. (previously presented) The method of claim 12 wherein the Factor XIIIa substrate comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15, and a combination or bioactive peptide fragment thereof.

14. (previously presented) The method of claim 13 wherein the Factor XIIIa substrate comprises an amino acid sequence of SEQ ID NO: 15.

16. (previously presented) The method of claim 10 wherein the growth factor is selected from the group consisting of VEGF, growth factors from the TGF-β superfamily, PDGF, IGF, and ephrin.

17. (previously presented) The method of claim 10 wherein the growth factor is selected from the group consisting of TGF-β1, BMP 2, $VEGF_{121}$, PDGF AB, L1Ig6, and a combination or bioactive peptide fragment thereof.

18. (previously presented) A bidomain protein or peptide comprising a transglutaminase substrate domain and a polypeptide growth factor.

19. (previously presented) The bidomain protein or peptide of claim 18 wherein the protein or peptide is a recombinant or synthetic protein or peptide.

20. (previously presented) The bidomain protein or peptide of claim 18 wherein the transglutaminase substrate domain is a Factor XIIIa substrate domain.

21. (previously presented) The bidomain protein or peptide of claim 20 wherein the Factor XIIIa substrate domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15, and combinations and bioactive fragments thereof.

22. (previously presented) The bidomain protein or peptide of claim 21 wherein the Factor XIIIa substrate domain comprises an amino acid sequence of SEQ ID NO: 15.

26. (previously presented) The bidomain protein or peptide of claim 18 wherein the growth factor is selected from the group consisting of VEGF, a growth factor from the TGF-β superfamily, PDGF, IGF, and ephrin.

27. (previously presented) The bidomain protein or peptide of claim 26 wherein the growth factor is selected from the group consisting of TGF-β1, $VEGF_{121}$, PDGF AB, BMP 2, and L1Ig6.

28. (previously presented) A matrix material for forming a gel comprising

(i) a bidomain protein or peptide comprising a transglutaminase domain and a polypeptide growth factor,

(ii) fibrinogen,

(iii) factor XIIIa, and

(iv) thrombin.

29. (previously presented) The matrix material of claim 28 wherein the transglutaminase substrate domain is a Factor XIIIa substrate domain.

30. (previously presented) The matrix material of claim 29 wherein the Factor XIIIa substrate domain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15, and combinations and bioactive fragments thereof.

34. (previously presented) The matrix material of claim 28 wherein the growth factor is selected from the group consisting of VEGF, a growth factor from the TGF-β superfamily, PDGF, IGF, and ephrin.

35. (previously presented) The matrix material of claim 34 wherein the growth factor is selected from the group consisting of TGF-β1, $VEGF_{121}$, PDGF AB, BMP 2, and L1Ig6.

Evidence Appendix

None

Related Proceedings Appendix

None